filing of the instant application. The amendment further states the field of the invention in a general manner, which was unintentionally omitted in the application as filed.

The amendment to the specification introduces no new matter. Enclosed herewith is a marked-up version of the changes made to the specification by this amendment. The enclosed page is captioned "**Version with markings to show changes made.**"

B. Claims

Claims 5-10, 12 and 17-20 are canceled, and new claims 26-40 are added. The newly added claims do not add new matter and are completely supported throughout the application as originally filed. More particularly, newly added claims 26-35, reciting a transgenic mouse comprising a disruption in a target gene, a method of producing said mouse, and cells or tissue isolated from said mouse can be found, for example, at page 8, line 4 through page 14, line 13, and at page 48, lines 9-24 of the specification. Support for the cells and tissue isolated from transgenic mice, which are recited in claims 30, 33, and 36 may further be found, for example, at page 2, lines 23-26 and at page 32, lines 8-21. Support for claims 37-40, recite *in vivo* methods of identifying agents that modulate prepulse inhibition and of identifying agents that ameliorate a phenotype associated with a disruption in a target gene may be found, for example, at page 17, line 14 through page 18, line 18 and at page 49, lines 10-14.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, claims 26-40 are pending in the instant application.

II. Rejections

A. Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 5-10, 12 and 17-20 under 35 U.S.C. § 112, first paragraph, asserting that the specification does not enable any person skilled the art to make and use the invention commensurate in scope with these claims. The rejection is respectfully traversed. However, in light of the cancellation of these claims, the Examiner's rejection is moot.

Newly added claims 26-40 are drawn to compositions and methods related to disruption of a target gene, as defined by the specification. Although the Applicant believes that ubiquitin specific protease as recited in claims 5-10, 12 and 17-20 is well defined in the instant application, the Applicant has cancelled these claims. The Applicant notes that the target gene referred to in newly added claims 26-40 is clearly defined and described in the specification, and such claims are fully enabled by the examples provided therein. In particular, the Applicant has provided in the specification a working example of such a disruption in the target gene using a targeting construct, which comprises as the targeting arms (homologous sequences) SEQ ID NO:2 and SEQ ID NO:3 (see page 48 of the specification and Figure 2B of the drawings). The Applicant notes that it is well known in the art of gene targeting that a targeting construct based on the target gene sequence as described in the specification would produce a disruption in the target gene. Undue experimentation would not be required for one skilled in the art to produce a disruption in the target gene, such as that recited in claims 26-40.

The Applicant submits that new claims 26-40 are fully enabled by the teachings of the specification, as noted above. As the rejections under 35 U.S.C. § 112, first paragraph, of claims 5-10, 12 and 17-20 are no longer relevant as a result of the cancellation of these claims, and new claims 26-40 are fully enabled by the teachings of the specification for the reasons stated above, the Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

B. Rejection under 35 U.S.C. § 112, second paragraph

Claim 5-7 and 12 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The rejection is respectfully traversed. However, in view of the cancellation of claims 5-7 and 12, the rejection is moot. The Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

The Applicant submits that new claims 26-40 are definite and particularly point out and distinctly claim the subject matter regarded as the invention in accordance with 35 U.S.C. § 112, second paragraph.

C. Rejection under 35 U.S.C. § 103

Claims 5-10 were rejected under 35 U.S.C. § 103 (a) as allegedly unpatentable over Capecchi, 1994, *Scientific American,* pages 52-59 ("Capecchi") taken with Woods *et al.,* 1997, *Mechanisms of Development* 63: 29-38 ("Woods"). The Applicant respectfully traverses this

rejection. However, in view of the cancellation of claims 5-10, the rejection under 35 U.S.C. § 103 (a) is no longer relevant.

The Applicant submits that new claims 26-40 are non-obvious over the teachings of the prior art references. The claimed invention relates to the *in vivo* mammalian characterization of the function of ubiquitin-specific protease genes, and, more particularly, the target gene described in the instant specification, and provides transgenic animals and cells comprising disruptions in the target gene and methods and compositions relating thereto, all of which are not obvious in view of the sole or combined teachings and disclosures of the references cited by the Examiner.

According to the Examiner, Capecchi teaches knockout technology applied to mice specifically with respect to the disruption of the *Hox*A-3 gene and as the method of producing the same applies to determining the *in vivo* biological function of any known gene of interest. Capecchi generally discusses the problems encountered in revealing the function of genes, and the challenges and benefits of using targeted disruptions in the mouse as a tool in discovering these functions. Capecchi further discloses a very general method of targeted gene replacement starting with creation of a targeting vector, introduction into mouse ES cells, selection and isolation of said cells, and generation of transgenic mice harboring the targeted gene replacement. Capecchi then further specifically discusses the effect or phenotype of a knockout of the *Hox*A-3 gene in mice observed in his laboratory, which revealed a role for *Hox*A-3 in development of the mouse embryo.

Capecchi, however, does not teach transgenic mice or cells comprising a disruption in a target gene such as the transgenic mice claimed by the present invention. Further, Capecchi does not teach the production of transgenic mice comprising disruptions in the target gene according to the instant invention, wherein the transgenic mice exhibit an increase in prepulse inhibition. In addition, Capecchi does not teach methods of using the transgenic mice for drug screening, as is presently claimed.

Woods, as characterized by the Examiner, teaches the cloning of a mouse nucleotide sequence that encodes a putative ubiquitin-specific protease, FAM, which shares extensive sequence homology with a *Drosophila* ubiquitin-specific protease, *faf*. The Examiner further asserts that Woods suggests a role for FAM in the developing embryo based on mRNA expression analyses during development.

Like Capecchi, the disclosure of Woods is deficient in teaching or suggesting any transgenic mouse, and, in particular, a transgenic mouse comprising a disruption in a target gene as currently claimed, or cells or tissue isolated from said mouse. Woods further lacks any methods of screening for agents using the transgenic mice.

Taken together, the disclosures of Capecchi and Woods are absent of any teaching or suggestion of disrupting the target gene of the instant invention in a mouse, and, in particular, are deficient of any teaching or suggestion of the transgenic mice, cells, tissue, and methods recited in the pending claims. More particularly, the disclosures of Capecchi and Woods, alone or in combination, do not teach or suggest in any way the transgenic mice comprising disrupted target genes, which exhibit increased prepulse inhibition, methods of producing such transgenic mice, tissues and cells isolated from such transgenic mice, and methods of using the transgenic mice to screen for agents, as is claimed by the present invention.

As the obviousness rejection is no longer relevant as a result of the cancellation of claims 5-10, and new claims 26-40 are not obvious in view of the teachings of Capecchi and Woods, the Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 103.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-456.

Respectfully submitted,

Date: 12/6/02

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CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify that this correspondence and its listed enclosures is being deposited with the United States Postal Service as First Class Mail, postage paid, in an envelope addressed to: Assistant Commissioner for Patents and Trademarks, Washington, D.C. 20231, Box Amendment on **December 6, 2002**

Name: **Deborah A. Mojarro**

Signed: Deborah A. Mojarro Date: 12/6/02

Version with Markings to Show Changes Made

Related Applications

~~**Field of the Invention**~~

This application claims priority to U.S. Provisional Application No. 60/217,350, filed July 11, 2000; U.S. Provisional Application No. 60/223,169, filed August 7, 2000; and U.S. Provisional Application ~~entitled *Transgenic Mice Containing Gene Disruptions*, Docket No. T-456b~~No. 60/301,214, filed June 26, 2001, the entire contents of which are incorporated herein by reference.

Field of the Invention

The present invention relates to transgenic animals, compositions and methods relating to the characterization of gene function.